1.0   TITLE PAGE

LVM-MD-14

A Double-blind, Placebo- and Active-controlled Evaluation of the Safety and Efficacy of Levomilnacipran ER in Pediatric Patients 7-17 Years with Major Depressive Disorder

STATISTICAL ANALYSIS PLAN

Final: 15 July 2019

Amendment #1: 21 April 2021

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3.0   **LIST OF ABBREVIATIONS**

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANTE(1)	First-order antedependence
AR(1)	First-order autoregressive
AST	Aspartate Aminotransferase
CDRS-R	Children's Depression Rating Scale–Revised
CS	Compound symmetry
COVID-19	Coronavirus disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition
ECG	Electrocardiogram, electrocardiographic
eCRF	Electronic case report forms
ITT	Intent-to-treat
LOCF	Last observation carried forward
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model for repeated measures
OC	Observed cases
PCS	Potentially clinically significant
PID	Patient identification
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula $(QTcB = QT/(RR)^{\frac{1}{2}})$

QTcF	QT interval corrected for heart rate using the Fridericia formula $(QTcF = QT/(RR)^{\frac{1}{3}})$
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SI	*Le Système International d'Unités* (International System of Units)
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TOEP	Toeplitz
TESAE	Treatment-emergent serious adverse event
ULN	Upper limit of normal

4.0   INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and specified in the protocol amendment #2 of Study LVM-MD-14 (dated 06 August 2020). Specifications of tables, figures, and data listings are contained in a separate document. The Modeling and Simulation Analysis Plan for pharmacokinetic will be prepared separately.

Study LVM-MD-14 is a Phase 3, multicenter, randomized, double-blind, placebo- and active-controlled, flexible-dose, parallel-group study in pediatric patients, ages 7-17 years, who have been diagnosed with major depressive disorder (MDD) using *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5) diagnostic criteria. The severity of MDD will be assessed based on Children's Depression Rating Scale – Revised (CDRS-R) scores, ranging in this study from 40 to 113.

The length of this study will be 10 weeks, including a 1-week screening/washout period, followed by an 8-week double-blind treatment period and a 1-week double-blind down-taper period. Signed informed consent from the patient or the patient's legally authorized representative and caregiver will be obtained before any study-related procedures are begun. All patients will be assigned a screening number. At the end of Visit 2 (Baseline), patients meeting the inclusion criteria will be randomized in 1:1:1 ratio to treatment groups of placebo, levomilnacipran, fluoxetine, respectively. A total of 480 patients (160 per treatment group) are planned to be randomized. Patients randomized to the levomilnacipran 40 – 80 mg/day group will receive 10 mg/day on Days 1-3, 20 mg/day on Days 4-7, and 40 mg/day during Weeks 2 through 8. Based on therapeutic response and tolerability, an additional dose increase to 80 mg/day is permitted at Week 3. During the down-taper period, patients will take levomilnacipran 40 mg/day for 2 days, and then levomilnacipran 20mg/day for 5 days. Patients randomized to the fluoxetine 20 mg/day group will receive fluoxetine 10 mg/day on Days 1-7, and then 20 mg/day during Weeks 2 through Week 8. During the down-taper period, patients will take fluoxetine 10 mg/day for 7 days. The dosing regimen and schedule for this study are presented in Table 4–1.

All randomized patients who complete the 8-week double-blind treatment period and patients who prematurely discontinue from the study before completing 8 weeks of double-blind treatment should enter the 1-week double-blind down-taper period when considered clinically appropriate by the investigator. Figure 4–1 provides a schematic of the study design.

Efficacy and safety assessments will be conducted at the clinic at the ends of Weeks 1, 2, 3, 4, 6, and 8 of double-blind treatment. Patients prematurely discontinuing from the study, regardless of cause, will be seen for a final evaluation. The schedule of evaluations for Study LVM-MD-14 is presented in Table 4–2.

Table 4–1.   Double-blind Daily Dosing Regimen

Treatment Group	Row	Week					
						Down-Taper	
		1		2	3-8	9/ET	
		Days 1-3	Days 4-7	Days 1-7	Days 1-7	Days 1-2	Days 3-7
Levomilnacipran 40 mg – 80 mg	A	LVM 10 mg	LVM 20 mg	LVM 40 mg	LVM 40 mg	LVM 40 mg	LVM 20 mg
	B	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
	A	Optional dose escalation to 80 mg as determined by treating physician			LVM 40 mg	LVM 40 mg	LVM 20 mg
	B				LVM 40 mg	Placebo	Placebo
Fluoxetine 20 mg	A	Fluoxetine 10 mg	Fluoxetine 10 mg	Fluoxetine 20 mg	Fluoxetine 20 mg	Fluoxetine 10 mg	Fluoxetine 10 mg
	B	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Placebo	A	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
	B	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

ET = Early termination; LVM = levomilnacipran
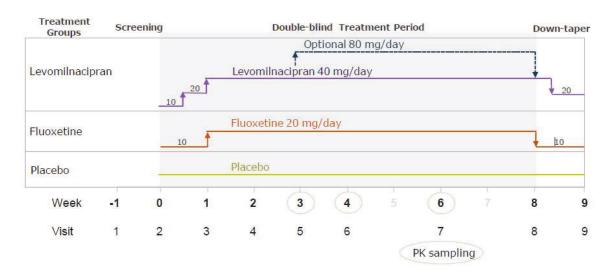
Figure 4–1.   Study Design

Table 4–2. Schedule of Evaluations: Study LVM-MD-14

	Screening Period	Double-blind Treatment Period							Double-blind Down-Taper Period
	Visit 1[a]	Visit 2 (Baseline)	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8/ ET[b]	Visit 9/SFU[c]
End of Study Week	–1	0	1	2	3	4	6	8	9
Informed assent (patient) and consent (parent[s]/legally authorized representative)	X								
Informed consent (caregiver)[d]	X								
Inclusion and exclusion criteria	X	X							
Determination of ability to swallow capsule	X								
Medical history	X								
Psychiatric history	X								
Medication history and non-drug psychiatric treatment history	X	X							
Concomitant medications			X	X	X	X	X	X	X
Physical examination	X[e]							X	
Clinical laboratory determinations	X[e]							X	
Serum β-hCG pregnancy test[f]	X[e]							X	
Thyroxine, TSH tests	X[e]								
Urine drug screen	X[e]								
ECG	X[e]				X			X	
Vital signs (BP, pulse, weight)		X	X	X	X	X	X		X
Vital signs (BP, pulse, weight and height[g])	X[e]							X	
K-SADS-PL[h]	X								
CDRS-R	X	X	X	X	X	X	X	X	
CGI-S	X	X	X	X	X	X	X	X	
CGI-I			X	X	X	X	X	X	
C-SSRS	X	X	X	X	X	X	X	X	X
PK sampling[i]					X	X	X		
AEs	X	X	X	X	X	X	X	X	X
IP dispensing		X	X	X	X	X	X	X[j]	
IP return			X	X	X	X	X	X	X[j]
IP compliance			X	X	X	X	X	X	X[j]

Note: If necessary, visits may be conducted up to 3 days before or after scheduled visits relative to the Baseline Visit (Visit 2).

a After assent and consent are obtained, the screening period may be up to 5 weeks in duration.

b   Visit 8 assessments to be completed for all randomized patients who complete the study or discontinue before Week 8.

c   All randomized patients must complete Visit 8/ET and, at the end of the down-taper period, return for Visit 9/SFU. Patients who do not enter the down-taper period must return for Visit 9/SFU approximately 1 week after Visit 8/ET Visit.

d   If the parent(s), guardian, or legally authorized representative (LAR) is also the patient's caregiver, he/she will be asked to sign both the parent and caregiver consents.

e   May be repeated at the Investigator's discretion before Visit 2.

f   A pregnancy test will be obtained for female patients of childbearing potential only.

g   Height will be recorded at Screening (Visit 1) and Visit 8/ET using a stadiometer.

h   K-SADS-PL data will be retained as source documents at the site.

i   ***PK only collected on patients aged 7-11 years.*** Sparse PK blood samples will be collected during Visit 5 (at predose and 1-4 hour postdose), Visit 6 (4-6 hours postdose), and Visit 7 (6-8 hours postdose). At Visit 5, or at any 24-hour period between Visit 5 and Visit 7, inclusive, serial blood samples will be collected from a subset of consented 7-11-year-old patients instead of sparse PK samples at the following time points: predose [20-24 hours after the most recent dose], and 2, 4, 6, 8, 10-12, and 24-hours postdose.

j   For patients entering the double-blind down-taper period.

AE = adverse event; β-hCG = β-human chorionic gonadotropin; BP = blood pressure; CDRS-R = Children's Depression Rating Scale–Revised; CGI-I = Clinical Global Impressions–Improvement (scale); CGI-S = Clinical Global Impressions–Severity (scale); C-SSRS = Columbia–Suicide Severity Rating Scale; ECG = electrocardiogram; ET = early termination; IP = investigational product; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime; LAR = legally authorized representative; PK = pharmacokinetic; SFU = Safety Follow-up; TSH = thyroid stimulating hormone

5.0   OBJECTIVES

The objective of this study is to evaluate the efficacy, safety, and tolerability of levomilnacipran compared with placebo in pediatric outpatients (7-17 years) with MDD.

In addition, the study is designed to obtain pharmacokinetic (PK) data to define the PK profile of levomilnacipran in the pediatric population (7-17 years of age).

6.0   PATIENT POPULATIONS

Four populations will be considered in the statistical analysis of the study as specified below.

6.1   SCREENED POPULATION

The Screened Population will consist of all patients who underwent a Screening Visit and received a screening number, and for whom informed consent was obtained.

6.2   RANDOMIZED POPULATION

The Randomized Population will consist of all patients in the Screened Population who were randomized to a treatment group in the study.

6.3   SAFETY POPULATION

The Safety Population will consist of all patients in the Randomized Population who received at least 1 dose of double-blind investigational product.

6.4   INTENT-TO-TREAT POPULATION

The Intent-to-Treat (ITT) Population will consist of all patients in the Safety Population who had the baseline and at least 1 postbaseline assessment of the CDRS-R total score.

7.0   PATIENT DISPOSITION

The number and percentage of patients in 3 of the study populations (Randomized, Safety, and ITT) will be summarized by treatment group and study center; the Screened Population will be summarized overall only by study center.

Screen-failure patients (i.e., patients screened but not randomized) and the associated reasons for failure to randomize will be tabulated overall for all the screened patients.

The number and percentage of patients who complete the double-blind treatment period and of patients who prematurely discontinue during the same period will be presented for each treatment group and pooled across treatment groups for the Safety Population. The number and percentage of patients who enter the double-blind down-taper period and of patients who complete the double-blind down-taper period will be presented for each treatment group and pooled across treatment groups for the Safety Population.

The reasons for premature discontinuation from the double-blind treatment period as recorded on the disposition pages of the electronic case report forms (eCRF) will be summarized (number and percentage) by treatment group for the Safety Population. Percentage of premature discontinuations will be provided for overall and for each discontinuation reason. All patients who prematurely discontinue during the double-blind treatment period will be listed by discontinuation reason for the Safety Population.

8.0   DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (age; age group [7-11 and 12-17]; sex; race; ethnicity), and baseline characteristics (weight; height; and body mass index (BMI)) will be summarized descriptively by treatment group for the Safety and ITT populations, respectively. Baseline efficacy variables will be summarized by treatment group for the ITT population.

Continuous variables will be summarized by number of patients and mean, SD, median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

Abnormalities in patients' medical and surgical histories will be coded using the *Medical Dictionary for Regulatory Activities (MedDRA)*, version 22.0 or newer. The number and percentage of patients with abnormalities in medical and surgical histories in each system organ class and preferred term will be summarized by treatment group for the Safety Population. MDD history and nondrug psychiatric treatment history will also be summarized by treatment group for the Safety Population.

The World Health Organization Drug Dictionary, version March 2017 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

Prior medication is defined as any medication taken before the date of the first dose of double-blind investigational product. *Concomitant medication* is defined as any medication taken on or after the date of the first dose of double-blind investigational product. Both prior and concomitant medications use will be coded by drug name and therapeutic class. The use of prior and concomitant medications will be summarized by the number and percentage of patients receiving each drug within each therapeutic class in each treatment group for the Safety Population. If a patient took a specific medication multiple times or took multiple medications within a specific therapeutic class, that patient would be counted only for the coded drug name or therapeutic class.

Summaries of concomitant medication use will be presented for the double-blind treatment period and the double-blind down-taper period, separately. Any concomitant medications started after the date of the last dose of double-blind investigational product in the study will not be presented in the summary tables but will be included in the patient data listings.

9.0   EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1   EXTENT OF EXPOSURE

Exposure to the investigational product for the Safety Population during the double-blind treatment period will be summarized in terms of treatment duration, calculated as the number of days from the date of the first dose of double-blind investigational product to the date of the last dose of double-blind investigational period, inclusive. Descriptive statistics (number of patients, mean, SD, median, Q1, Q3, minimum, and maximum) will be presented by treatment group. The number and percentage of patients will be presented for specific intervals of exposure by treatment group.

Patient-years, defined as total exposure to the double-blind investigational product in years (excluding the double-blind down-taper period), will be summarized by treatment for the Safety Population.

In addition, weekly and overall mean daily dose of investigational product during the double-blind treatment period will be summarized by treatment group for the Safety population.

9.2   MEASUREMENT OF TREATMENT COMPLIANCE

Dosing compliance for a specified period is defined as the number of capsules actually taken by a patient during that period divided by the number of capsules prescribed for the same period multiplied by 100. The total number of capsules actually taken during a specific time period will be calculated from the study medication records. The number of capsules expected to be taken for a specific treatment period will be calculated by multiplying the number of days in that period by the number of capsules prescribed to be taken per day.

Descriptive statistics for investigational product compliance during the double-blind treatment period will be presented by treatment group for each period between 2 consecutive visits, as well as for the whole double-blind treatment period, for the Safety Population.

10.0   EFFICACY ANALYSES

The efficacy analyses will be based on the ITT Population. *Baseline* for efficacy is defined as the last non-missing efficacy assessment recorded at or prior to first dose of investigational product. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

For efficacy analyses in which study center is a factor, a small center will be defined as a center with fewer than 2 patients in any treatment group in the ITT Population. Small centers will be pooled to form pseudo-centers so that each treatment group includes at least 2 ITT patients within the center. Pooling will be done using the following algorithm:

Based on the number of ITT patients, small centers will be ordered from the largest to the smallest, and centers of the same size will be ordered from the largest center code to the smallest center code. The pooling process starts with the largest small center from the top, hich will be pooled with the smallest from the bottom until a non-small pseudo center is formed. The process will be repeated using the small centers left out after the first pass. If any centers are left out at the end of the process, they will be pooled with the smallest pseudo center. If there is more than 1 smallest pseudo center, the pseudo center with the smallest center code will be selected. In case that the pseudo center formed by pooling all small centers is still a small center, it will be pooled with the smallest non-small center. If there is more than 1 smallest non-small center, the one with the smallest center code will be selected.

These pseudo-centers will be used for all efficacy analyses when the model is adjusted for study center.

By-visit analyses based on the mixed-effects model for repeated measures (MMRM) using the observed case (OC) approach will be performed for all continuous efficacy parameters with multiple post-baseline measurements.

In addition, by-visit analyses using the last-observation-carried-forward (LOCF) approach will be presented for all efficacy parameters. For the LOCF approach, only the postbaseline total score of a parameter will be imputed; individual item scores will not be carried forward to derive the total score. Baseline total score will be carried forward only for the intermittent missing scores immediately after baseline. If all the postbaseline values are missing, the baseline value will not be carried forward.

10.1   PRIMARY EFFICACY PARAMETER(S)

The primary efficacy parameter will be the change from baseline in CDRS-R total score at Week 8. The primary analysis for comparing levomilnacipran vs. placebo for the primary efficacy parameter will be performed using an MMRM with treatment group,

pooled study center, visit, and treatment group-by-visit interaction as fixed effects and the baseline value and baseline value-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The Kenward-Roger approximation (Kenward and Roger, 1997) will be used to estimate denominator degrees of freedom. This analysis will only use the observed cases of postbaseline scores without imputation of missing values. In the event of non-convergence of the model using unstructured covariance matrix, a structured covariance matrix will be used in combination with empirical variance estimate (i.e. sandwich estimator) to address the potential mis-specified situation. The following sequence of alternative covariance structures (First-order antedependence [ANTE (1)], Toeplitz [TOEP], First-order autoregressive [AR(1)] and compound symmetry[CS]) will be considered in the MMRM until convergence.

To control the overall type I error rate for the multiple comparisons across the primary and the secondary hypotheses, a fixed sequence procedure will be applied. Details are provided in Section 10.2.

In addition, two sensitivity analyses, LOCF and pattern-mixture model approaches, will be performed on the primary efficacy parameter.

The LOCF approach is based on an analysis-of-covariance (ANCOVA) model including treatment group and pooled study center as factors and baseline CDRS-R total score as a covariate. The pattern-mixture model approach is based on the non-future dependent missing value restrictions (Kenward et al., 2003) and is performed to assess the robustness of the primary MMRM results to the possible violation of the missing-at-random assumption. The pattern for the pattern-mixture model will be defined by the patient's last visit with an observed value. The observed CSRS-R total score at a visit is assumed to have a linear relationship with the patient's prior measurements. The missing values will be imputed under the assumption that the distribution of the missing observations differs from that of the observed only by a shift parameter value Δ. The dataset with all missing values imputed will be analyzed using an ANCOVA model with treatment group and pooled study center as factors and baseline CDRS-R total score as a covariate for between-treatment group comparisons at Week 8. The imputation of missing values and the analysis will be performed multiple times and the inference of this sensitivity analysis will be based on the combined estimates using the standard multiple imputation technique. The range of values for the shift parameter Δ is selected as 0 to 6 based on experience with historical data. Technical details of the proposed pattern-mixture model approach (e.g., the models for the pattern-specific identifiable densities and the unidentified conditional distributions, the shift parameter Δ, and the multiple imputation algorithm) are provided in Appendix I to this SAP.

Graphical display of treatment difference vs. placebo (mean difference ± SE) in primary efficacy parameter will be provided by pooled study center to examine the consistency of the primary efficacy results across study centers.

The site 0070 ceased operations on October 31, 2020, due to the damage caused by Hurricanes Laura and Delta, which made landfall on August 27, 2020 and October 10, 2020, respectively. One more sensitivity analysis excluding all data from this site will be performed on the primary efficacy parameter. The same MMRM would be applied on all OC of change from baseline to Week 8 in CDRS-R total score except all values of Site 0070.

10.2   SECONDARY EFFICACY PARAMETER(S)

The secondary efficacy parameter is the change from baseline to Week 8 in CGI-S score, which will be analyzed using the MMRM approach similar to the one used for the primary efficacy parameter. A sensitivity analysis will also be performed using the LOCF approach as described in Section 10.1.

To control the overall family-wise type I error rate for multiple comparisons across the primary and the secondary efficacy parameters, the fixed sequence testing procedure will be implemented, i.e., the efficacy analysis of the secondary efficacy parameter will be carried out inferentially only if the null hypothesis for the primary efficacy parameter is rejected.

10.3   ADDITIONAL EFFICACY PARAMETER(S)

The additional efficacy parameters will include the following at each postbaseline visit:

- CGI-I score

- Change from baseline in CGI-S score

- CDRS-R response ($\geq$ 40% reduction in CDRS-R from baseline) rate

- CDRS-R remission (CDRS-R $\leq$ 28) rate

The CGI-I score and change from baseline in CGI-S score will be analyzed using the MMRM and the LOCF approaches similar to the ones used for the primary efficacy parameter. For the analysis of CGI-I score, the baseline CGI-S score will be used as the baseline variable.

The CDRS-R response rate and CDRS-R remission rate will be analyzed using a generalized linear mixed model (GLMM), based on a logit link function, with a random intercept and fixed effect terms of treatment group, visit, treatment-by-visit interaction, and baseline score. If the GLMM does not converge, a logistic regression model with treatment group and baseline score as explanatory variables will be used. For the logistic regression analysis, postbaseline missing data will be imputed using the LOCF approach.

In addition, plots of changes from baseline in CDRS-R total score will be presented across study visits by treatment group.

11.0   SAFETY ANALYSES

The safety analysis will be performed for the double-blind treatment period and the double-blind down-taper period (only for safety parameters collected during the double-blind down-taper period), separately, using the Safety Population unless stated otherwise.

The safety parameters will include adverse events (AEs) and clinical laboratory parameters, vital sign measurements, electrocardiographic (ECG) parameters, suicide risk assessment using the Columbia-Suicide Severity Rating Scale (C-SSRS), and growth evaluation. For each safety parameter, the last nonmissing safety assessment before the first dose of investigational product will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of patients and mean, SD, median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

For patients who take the double-blind down-taper investigational product, the double-blind treatment period starts with the first dose of double-blind investigational product and ends with the last assessment date up to the first dose of the double-blind down-taper investigational product. The double-blind down-taper period starts one day after the end of the double-blind treatment period and ends with the latter of the last dose of the double-blind down-taper investigational product and the last assessment date.

For patients who do not take the double-blind down-taper investigational product, the double-blind treatment period starts with the first dose of double-blind investigational product and ends with the latter of the last dose of the double-blind investigational product and the last assessment date.

11.1   ADVERSE EVENTS

Adverse events will be coded by system organ class and preferred term using the *MedDRA,* version 22.0 or newer.

An AE will be considered a treatment-emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the date of the first dose of investigational product. However, an AE that occurs more than 30 days after the last dose of study intervention will not be counted as a TEAE. Per eCRF instructions, a new AE record will be created with a new AE onset date for any AE that worsens. Therefore, TEAEs can simply be identified as those AEs with recorded onset date on or after the date of the first dose of investigational product and within 30 days after the last dose of investigational product. If more than 1 AE was reported before the date of the first dose of investigational product and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the double-blind treatment period or during the double-blind down-taper period that were also coded to that preferred term.

The number and percentage of patients reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term and further categorized by severity and causal relationship to the investigational product, for both the double-blind treatment period and the double-blind down-taper period, separately. If more than 1 AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the greatest severity and strictest causality for the summarization by severity and by causal relationship to the investigational product, respectively.

The distribution of TEAEs by severity and causal relationship to the investigational product will be summarized by treatment group separately for the double-blind treatment period and the double-blind down-taper period. Common TEAE during the double-blind treatment period is defined in 2 ways: $\geq 1\%$ of patients in any treatment group and $\geq 2\%$ of patients in any treatment group. The incidence of common TEAEs will be summarized separately by preferred term, and treatment group and will be sorted by decreasing frequency for the levomilnacipran treatment group.

An AE will be considered a treatment-emergent serious adverse event (TESAE) if it is a TEAE that additionally meets any serious adverse event (SAE) criterion.

The number and percentage of patients who have TESAEs will be summarized by preferred term and treatment group and will be sorted by decreasing frequency for the levomilnacipran treatment groups.

The number and percentage of patients in the Safety Population who have AEs leading to premature discontinuation of the investigational product will be summarized by preferred term and treatment group and will be sorted by decreasing frequency for the levomilnacipran treatment group.

Listings will be presented for patients with SAEs, patients with AEs leading to discontinuation, and patients who died (if any) for the Screened Population. All patients with SAEs, including those reported during the screening period or more than 30 days after the date of the last dose of the double-blind investigational product, and patients discontinuing because of AEs before taking double-blind investigational product will be included in these listings.

11.2   CLINICAL LABORATORY PARAMETERS

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment time point (including the end of the double-blind treatment period) will be presented by treatment group for the following laboratory parameters:

Hematology: Absolute and differential white blood cell count, erythrocyte count, hemoglobin, hematocrit, platelet count, and red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration)

Chemistry: Sodium, potassium, calcium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total protein, alkaline phosphatase, albumin, total bilirubin, direct bilirubin, indirect bilirubin, AST, ALT, Free T3, free T4, TSH, lactate dehydrogenase, creatine phosphokinase, γ-glutamyl transpeptidase, uric acid, phosphate, lipid panel (total cholesterol, triglycerides, low density lipoproteins, high density lipoproteins), prolactin, insulin, and magnesium

Urinalysis: Specific gravity, pH, protein, glucose

In addition, descriptive statistics for values and changes from the baseline values in conventional units at each assessment time point will be presented for selected clinical laboratory parameters listed in Appendix II.

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table 11–1. The number and percentage of patients who have PCS postbaseline clinical laboratory values will be tabulated by treatment group. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive listing of patients with PCS postbaseline values will be provided, including the patient identification (PID) number, and baseline and all postbaseline (including non-PCS) values. In addition, a listing of all AEs that occurred in patients who had PCS postbaseline clinical laboratory values will be provided.

Table 11–1   Criteria for Potentially Clinically Significant Laboratory Values

Parameter	SI Unit	Lower Limit	Higher Limit
HEMATOLOGY			
Basophils	%	—	> 6
Eosinophils	%	—	> 10
Hematocrit	ratio	< 0.9 × LLN	—
Hemoglobin	g/L	< 0.9 × LLN	—
Lymphocytes	%	< 10	> 60
Monocytes	%	—	> 20
Neutrophils	%	< 30	> 90
Platelet count	× 10^9/L	≤ 75	≥ 700
White blood cell count	× 10^9/L	≤ 2.5	≥ 15
CHEMISTRY			
Albumin	g/L	< 0.9 × LLN	> 1.1 × ULN
Alkaline phosphatase	U/L	—	≥ 3 × ULN
Alanine aminotransferase	U/L	—	≥ 3 × ULN
Aspartate aminotransferase	U/L	—	≥ 3 × ULN
Bicarbonate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Blood urea nitrogen	mmol/L	—	> 1.2 × ULN
Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Chloride	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Cholesterol, total	mmol/L	—	> 1.3 × ULN
Creatinine	µmol/L	—	> 1.3 × ULN
Glucose	mmol/L	< 0.8 × LLN	> 1.4 × ULN
High-density lipoprotein	mmol/L	< 0.8 × LLN	—
Low-density lipoprotein	mmol/L	—	> 2.0 × ULN
Magnesium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Phosphate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Potassium	mmol/L	< 1.0 × LLN	> 1.0 × ULN
Sodium	mmol/L	< 1.0 × LLN	> 1.0 × ULN
Total bilirubin	µmol/L	—	> 1.5 × ULN
Total protein	g/L	< 0.9 × LLN	> 1.1 × ULN
Triglyceride	mmol/L	—	> 3.0 × ULN
URINALYSIS			
Protein	mg/dL	—	at least 2 +
Glucose	mmol/L	—	at least 2 +

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; LLN = lower limit of normal value provided by the laboratory; PCS = potentially clinically significant; SI = Le Système International d'Unités (International System of Units); ULN = upper limit of normal value provided by the laboratory.

Shift tables from baseline to end of double-blind treatment period for clinical laboratory parameters will be presented by treatment group for the following categories: low, normal, and high.

Potential Hy's Law criteria is defined by a postbaseline elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq$ 3x ULN (ULN = upper limit of normal laboratory reference range), along with total bilirubin (TBL) $\geq$ 2x ULN and a non-elevated alkaline phosphatase (ALP) < 2x ULN, all based on blood draws collected within a 24-hour period. The number and percentage of patients who meet the following criteria of clinical interest during the double-blind treatment period will be tabulated by treatment group. A supportive list will also be provided.

- ALT: $\geq$ 3x ULN, $\geq$ 5x ULN, $\geq$ 10x ULN, $\geq$ 20x ULN

- AST: $\geq$ 3x ULN, $\geq$ 5x ULN, $\geq$ 10x ULN, $\geq$ 20x ULN

- ALT or AST: $\geq$ 3x ULN, $\geq$ 5x ULN, $\geq$ 10x ULN, $\geq$ 20x ULN

- TBL: $\geq$ 2x ULN

- ALP: $\geq$ 1.5x ULN

- Concurrent elevations: ALT or AST $\geq$ 3x ULN with TBL $\geq$ 1.5x ULN; ALT or AST $\geq$ 3x ULN with TBL $\geq$ 2x ULN; ALT or AST $\geq$ 3x ULN with TBL $\geq$ 2x ULN and ALP < 2x ULN.

11.3   VITAL SIGNS

Descriptive statistics for vital signs (sitting radial pulse rate, sitting systolic and diastolic blood pressure, body weight and height) and changes from baseline values at each visit, and at the end of double-blind treatment period, and at the end of double-blind down-taper period will be presented by treatment group. Only patients with available baseline and at least 1 postbaseline assessment will be included in the summary. Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline criteria listed in Table 11–2. The number and percentage of patients with PCS postbaseline values will be tabulated by treatment group separately for the double-blind treatment period and the double-blind down-taper period. The percentages will be calculated relative to the number of patients with available baseline and at least 1 postbaseline assessment. The numerator will be the total number of patients with available baseline values and at least 1 PCS postbaseline value. A supportive listing of patients with PCS postbaseline values will be provided, including the PID number, and baseline and all postbaseline (including non-PCS) values.

In addition, a listing of all AEs that occurred in patients who had PCS postbaseline vital sign values will be provided.

Table 11–2. **Criteria for Potentially Clinically Significant Vital Signs**

Parameter	Flag	Criteria[a]	
		Observed Value	**Change From Baseline**
Sitting systolic blood pressure, mm Hg	High	≥ 140	Increase of ≥ 20
	Low	≤ 80	Decrease of ≥ 20
Sitting diastolic blood pressure, mm Hg	High	≥ 100	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Sitting pulse rate, bpm	High	≥ 130	Increase of ≥ 15
	Low	≤ 45	Decrease of ≥ 15
Weight, kg	High	—	Increase of $\geq 7\%$
	Low	—	Decrease of $\geq 7\%$

a   A postbaseline value is considered potentially clinically significant if it meets both the observed-value and the change-from-baseline criteria.

bpm = beats per minute.

11.4 ELECTROCARDIOGRAM

Descriptive statistics for ECG parameters (heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc) at baseline and changes from baseline values at each assessment time point (including the end of the double-blind treatment period) will be presented by treatment group. The QTc will be calculated using both the Bazett and Fridericia corrections. Only patients with available baseline and at least 1 postbaseline assessment will be included in the summary.

Electrocardiographic parameter values are considered PCS if they meet or exceed the higher-limit PCS criteria listed in Table 11–3. The number and percentage of patients with PCS postbaseline ECG values will be tabulated by treatment group for the double-blind treatment period. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment for the double-blind treatment period. The numerator is the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value for the double-blind treatment period. A supportive tabular display of patients with PCS postbaseline values will be provided, including the PID number, baseline, all postbaseline (including non-PCS) values, and change from baseline.

In addition, a listing of all AEs that occurred in patients who had postbaseline PCS ECG values will be provided.

Table 11–3.   **Criteria for Potentially Clinically Significant Electrocardiograms**

Parameter	Unit	Higher Limit
QRS interval	msec	≥ 150
PR interval	msec	≥ 250
QTcB	msec	>500
QTcF	msec	> 500

QTcB = QT interval corrected for heart rate using the Bazett formula (QTcB=QT/(RR)$^{1/2}$); QTcF = QT interval corrected for heart rate using the Fridericia formula (QTcF=QT/(RR)$^{1/2}$)

A listing of patients with postbaseline clinically significant ECG abnormalities as reported by the central laboratory and the Investigators will be provided.

The number and percentage of patients with an increase > 30 msec but ≤ 60 msec, and with an increase > 60 msec in QTcB or QTcF will be tabulated. A supportive listing of patients with postbaseline QTcB or QTcF increases > 30 msec will be provided, including the PID number, and all QTcB and QTcF values (including changes from baseline). A listing of all AEs for patients with postbaseline QTcB or QTcF increases > 30 msec will also be provided.

A shift table from baseline to the end of double-blind treatment period in the Investigator's overall interpretation of the ECG will be presented by treatment group for the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant.

11.5   OTHER SAFETY PARAMETERS

Other safety parameters include Columbia-Suicide Severity Rating Scale (C-SSRS) and growth.

11.5.1   Columbia-Suicide Severity Rating Scale

For the C-SSRS, the number and percentage of patients with any suicidal ideation or suicidal behavior at Baseline (lifetime history), and during the double-blind treatment period and during double-blind down-taper period will be summarized by treatment group for the Safety population. The distribution of responses for the most severe suicidal ideation and the most severe suicidal behavior will also be summarized by treatment group, separately for the lifetime history, the double-blind treatment period, and the double-blind down-taper period. Supportive listings will be provided and will include the PID number, treatment group, visit number, lifetime history, and postbaseline values for each patient. Intensity of ideation, suicidal behavior type, and lethality of suicidal behavior will also be included in these listings. A listing of all AEs occurring in patients who have suicidal ideation or suicidal behavior will also be provided.

11.5.2   Growth Evaluation

Weight and height will be presented as standardized z-scores adjusted for gender and age, using the LMS method (Cole T.J., 1990).

To assess the impact of treatment on growth, the change from baseline to Week 8 in the age-and-gender-adjusted height and weight will be analyzed using an ANOVA model with treatment as factor. A non-parametric (Wilcoxon) test will also be performed.

12.0   HEALTH OUTCOMES ANALYSES

Not applicable.

13.0   **INTERIM ANALYSIS**

The interim analysis will be conducted when at least 50% of randomized patients have either completed or discontinued the study. A futility analysis and safety analysis will be included in the interim analysis listed in the Appendix III. The general data derivation and preparation will follow the specification in the SAP and the amendment.

The futility assessment of the primary efficacy parameter (CDRS-R total score) on ITT population will be based on the conditional power as described in Lan et al. (1988) and Proschan et al. (2006). In calculating the conditional power, it is assumed that the future patients to be enrolled into the Study will have similar efficacy as those of the existing patients of the same treatment group. The non-binding futility criteria will be met when the conditional power for detecting a statistically significant treatment difference between the levomilnacipran treatment group (40-80 mg/day) and placebo at the final analysis given the interim analysis results is 0.2 (20%) or lower. Further details of the calculation of conditional power are provided in Appendix IV.

The safety analysis will be performed on the Safety Population, including the summary of TEAE, SAE, death, and TEAE leading to study discontinuation; the incidence of common TEAEs ($\geq$ 2%); PCS for laboratory parameters, vital signs, and ECGs; and the summary of C-SSRS during the double-blind treatment period.

Data will be presented in an unblinded fashion. A separate, independent, fire-walled Statistical Analysis Group and Data Review Committee will be established to conduct the unblinded interim analysis, review the unblinded results and make recommendations regarding the continuation of the study. To maintain the scientific reliability of statistical analyses after the final database lock, preserve the integrity of study conduct, and guard from introducing any potential bias into the conduct of the study and/or analysis of its results, individuals in these two groups will not be involved in any operational aspects of the trial.

14.0   DETERMINATION OF SAMPLE SIZE

The effect size (treatment group difference relative to pooled SD) of 0.36 for both levomilnacipran and fluoxetine is based on a treatment difference of 4 units with a common pooled SD of 11.1 for the primary efficacy parameter, change from baseline to Week 8 in CDRS-R total score. A sample size of 480 patients (160 per treatment group) will be needed to provide 85% power for primary analysis (levomilnacipran vs. placebo) based on an MMRM model using simulation method (Lu, 2012). The simulation assumed a correlation of 0.7 between the repeated measures and a dropout rate of 17% based on historical data in pediatric patients.

15.0   STATISTICAL SOFTWARE

Statistical analyses will be performed using version 9.4 (or newer) of SAS on a Linux operating system.

16.0   DATA HANDLING CONVENTIONS

16.1   VISIT TIME WINDOWS

Table 16–1 and Table 16–2 present the visits assigned for efficacy and safety analyses and the corresponding range of treatment days (window) during which an actual visit may occur.

Table 16–1.   Visit Time Windows for Double-Blind Treatment Period

Derived Visit	Scheduled Visit Day[a]	Window
Baseline	Week 0 (Day 1)	Days ≤ 1
Week 1	End of Week 1 (Day 8)	Days [2, 11]
Week 2	End of Week 2 (Day 15)	Days [12, 18]
Week 3	End of Week 3 (Day 22)	Days [19, 25]
Week 4	End of Week 4 (Day 29)	Days [26, 35]
Week 6	End of Week 6 (Day 43)	Days [36, 49]
Week 8	End of Week 8 (Day 57)	Days ≥ 50 days and within double-blind treatment period
End of double-blind treatment period[b]	Final or Termination Visit during the double-blind treatment period	

a   Relative to the date of the first dose of double-blind investigational product. Day 1 = the date of the first dose of double-blind investigational product. There is no Day 0 or Week 0.

b   Presented in analysis tables for safety parameters, including but not limited to electrocardiograms, clinical laboratory values, and vital signs, and C-SSRS. If repeat assessments occur at the end of double-blind treatment period visit, the algorithm in Section 16.4 will be used to determine which values are used in the analysis.

Table 16–2.   Visit Time Windows for the Double-Blind Down-Taper period

Derived Visit	Scheduled Visit	Window
Week 9	End of Week 9	Within the double-blind down-taper period (from 1 day after the end of double-blind treatment period to the end of the double-blind down-taper period)
End of double-blind down-taper period[a]	Final of termination visit during the double-blind down-taper period.	

a   Presented in analysis tables for safety parameters collected during the double-blind-down-taper period. If any assessments are repeated at the end-of-double-blind-down-taper-period visit, the algorithm in Section 16.4 will be used to determine which values are used in the analysis.

If the visit date is on or after the date of the first dose of double-blind investigational product, the study day is calculated by visit date – date of the first dose of double-blind investigational product +1. If the visit date is before the date of the firs dose of double-blind investigational product, the study day is calculated by visit date – date of the first dose of double-blind investigational product. Therefore, a negative day indicates a day before the start of the double-blind investigational product.

If a patient has 2 or more visits within the same window, the last visit with a nonmissing value will be used for analysis.

16.2 DERIVED EFFICACY VARIABLES

If a patient misses a postbaseline visit or if his/her postbaseline visit is outside of the visit time window, a record for the scheduled visit will be imputed using the last observed nonmissing value immediately before the missing value. If the missing value occurs at Week 1, the baseline value will be carried forward for Week 1, provided that at least 1 subsequent postbaseline assessment is available. For a composite scale such as CDRS-R total score, individual items of the rating scale will not be carried forward. Only total scores will be carried forward using the LOCF approach.

16.3 AGE-AND-GENDER-CORRELATED VALUES FOR WEIGHT AND HEIGHT

To adjust weight (kg) and height (cm) for sex and age, one needs to compare them to standard reference values for the same sex and age group, which are available in the United States Growth Charts and can be downloaded from: http://www.cdc.gov/growthcharts/percentile_data_files.htm.

The z-score is calculated as below

$$z = \frac{(X/M)^L - 1}{SL}, \text{ if L} \neq 0 \text{ and}$$

$$z = \frac{\ln(X/M)}{S}, \text{ if } L = 0,$$

where X is the physical measurement (e.g. weight and height) and L, M and S are the values from the appropriate table corresponding to the age in months (or length/stature) and sex (1 = male; 2 = female). X must be in metric measurements (kilograms or meters). This is called LMS method (Cole TJ, 1990), and parameters L, M, and S are the Box-Cox transformation power, median, and standard deviation, respectively, in the reference data, which again are provided in the reference data tables.

**16.4   REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY
                 PARAMETERS**

If a patient has repeated assessments before the date of first dose of double-blind
treatment period the results from the final nonmissing assessment made before the date of
the first dose of double-blind investigational product will be used as baseline. If end-of-
double-blind-treatment period assessments are repeated or if unscheduled visits occur, the
last nonmissing postbaseline assessment during the double-blind treatment period will be
used as the end-of-double-blind-treatment-period assessment for generating summary
statistics. Likewise, if end of double-blind down-taper period assessments are repeated or
if unscheduled visits occur, the last non-missing assessment during the double-blind
down-taper period will be used as the end-of-double-blind-down-taper-period assessment
for generating summary statistics. However, all postbaseline assessments will be used to
determine PCS values for laboratory parameters, vital signs and ECG parameters, and to
determine most severe suicidal ideation and most severe suicidal behavior from C-SSRS.
All assessments will be presented in the data listings.

**16.5   MISSING DATE OF THE LAST DOSE OF
                 INVESTIGATIONAL PRODUCT**

When the date of the last dose of investigational product in the study taken during the
double-blind treatment period is missing for a patient in the Safety Population, all efforts
should be made to obtain the date from the Investigator. If after all efforts are made it is
still missing, the last available dosing record date will be used as the last dose date.

16.6   MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the first dose of double-
blind investigational product, an intensity of mild will be assigned. If severity is missing
for an AE that started on or after the date of the first dose of double-blind investigational
product, an intensity of severe will be assigned. The imputed values for severity
assessment will be used for the incidence summary; the values will be shown as missing
in the data listings.

**16.7   MISSING CAUSAL RELATIONSHIP TO STUYD DRUG FOR
                 ADVERSE EVENTS**

If the causal relationship to the investigational product is missing for an AE that started
on or after the date of the first dose of investigational product, a causality of yes will be
assigned. The imputed values for causal relationship to investigational product will be
used for the incidence summary; the values will be shown as missing in the data listings.

16.8   **MISSING DATE INFORMATION FOR ADVERSE EVENTS**

The following imputation rules only apply to cases in which the start date for AEs is incomplete (i.e., partly missing).

Missing month and day
- If the year of the incomplete start date is the same as the year of the first dose of study double-blind investigational product, the month and day of the first dose of double-blind investigational product will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of double-blind investigational product, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of double-blind investigational product, *January 1* will be assigned to the missing fields

Missing month only
- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only
- If the month and year of the incomplete start date are the same as the month and year of the first dose of double-blind investigational product, the day of the first dose of double-blind investigational product will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of double-blind investigational product or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of double-blind investigational product, the last day of the month will be assigned to the missing day

- If either the year of the incomplete start date is after the year of the date of the first dose of double-blind investigational product or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of double-blind investigational product, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of double-blind investigational product, the date of the first dose of investigational product will be assigned to the missing start date

- If the stop date is before the date of the first dose of double-blind investigational product, the stop date will be assigned to the missing start date

16.9   MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, including rescue medications, incomplete (i.e., partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a patient, the start date will be imputed first and then the stop date will be imputed. If the imputed started date is after the imputed stop date, the imputed stop date will be adjusted by imputed start date.

16.9.1   Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day
- If the year of the incomplete start date is the same as the year of the first dose of double-blind investigational product, the month and day of the first dose of investigational product will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of double-blind investigational product, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of double-blind investigational product, *January 1* will be assigned to the missing fields

Missing month only
- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only
- If the month and year of the incomplete start date are the same as the month and year of the first dose of double-blind investigational product, the day of the first dose of investigational product will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of double-blind investigational product or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of double-blind investigational product, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of the first dose of double-blind investigational product or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of double-blind investigational product, the first day of the month will be assigned to the missing day

16.9.2   Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of double-blind investigational product is missing, impute it as described in Section 16.4. If the imputed stop date is before the start date (imputed or non-imputed start date), the imputed stop date will be equal to the start date.

Missing month and day
- If the year of the incomplete stop date is the same as the year of the last dose of investigational product during double-blind treatment period, the month and day of the last dose of investigational product will be assigned to the missing fields

- If the year of the incomplete stop date is before the year of the last dose of investigational product during double-blind treatment period, *December 31* will be assigned to the missing fields

- If the year of the incomplete stop date is after the year of the last dose of investigational product during double-blind treatment period, *January 1* will be assigned to the missing fields

Missing month only
- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of investigational product during double-blind treatment period, the day of the last dose of investigational product will be assigned to the missing day

- If either the year of the incomplete stop date is before the year of the date of the last dose of investigational product during double-blind treatment period or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of investigational product during double-blind treatment period, the last day of the month will be assigned to the missing day

- If either the year of the incomplete stop date is after the year of the date of the last dose of investigational product during double-blind treatment period or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of investigational product during double-blind treatment period, the first day of the month will be assigned to the missing day

16.10   CHARACTER VALUES OF CLINICAL LABORATORY PARAMETERS

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings.

Table 16–3 shows examples of how some possible laboratory results should be coded for the analysis.

Table 16–3.   Examples of Coding Special Character Values for Clinical Laboratory Parameters

Laboratory Test, SI Unit	Possible Laboratory Results	Coded Value for Analysis
CHEMISTRY		
ALT, U/L	< 5	5
AST, U/L	< 5	5
Bilirubin, total, µmol/L	< 2	2
URINALYSIS		
Glucose, mmol/L	< 2.775, Negative	0
	[2.775, 5.55)	1+
	[5.55, 13.875)	2+
	[13.875, 27.75)	3+
	[27.75, 55.5)	4+
	$\geq$55.5	5+
Ketones, mmol/L	> 0.444, $\geq$ 0.444, > 0, Trace	Positive
	$\leq$ 0, Negative	Negative
pH	> 8.0, $\geq$ 8.0	8.0
	$\geq$ 8.5	8.5
Protein g/L	< 0, Negative	Negative
	[0, 0.15), Trace	0
	[0.15, 0.3)	1+
	[0.3, 1.0)	2+
	[1.0, 5.0)	3+
	$\geq$ 5.0	4+

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SI = *Le Système International d'Unités* (International System of Units).

17.0   COVID-19 RELATED ANALYSIS

To eliminate immediate potential hazards to patients and study staff due to the COVID-19 pandemic while ensuring patients safety and maintaining data integrity, the protocol amendment #2 has been sent to sites to allow remote visits.

This section specifies analyses for evaluating the impact of COVID-19.

17.1   EFFICACY EVALUATION

Due to the nature of the patient CDRS-R assessment, the interview may be performed remotely provided that the patient has access to a videoconferencing platform where the rating clinician can visually see the patient during the discussion. Minimal disruption is expected for this endpoint.

17.2   SAFETY AND OTHER EVALUATION

This section specifies analyses related to the COVID-19 pandemic from the following aspects:

- Disposition

- Study visit (missing entire visit due to COVID-19 or missing assessments due to COVID-19)

- Protocol deviation

- Study drug disruption due to COVID-19

- TEAEs related to COVID-19

The Safety Population will be used for the planned analyses described above.

The number of patients impacted by COVID-19 during the study will be summarized by treatment group and overall. In addition, the number of patients impacted by COVID-19 and their corresponding disposition status in the double-blind treatment period, down-taper period, and follow-up period will be summarized, respectively.

The number of patients who missed at least one entire visit due to COVID-19 will be summarized by treatment group and overall. Furthermore, the number of patients who missed at least one assessment due to COVID-19 will be summarized by assessment category (laboratory, C-SSRS, vital signs, and ECG) and overall. Similar summarized will by provided by visit.

The protocol deviations that occur due to COVID-19 will be summarized and listed separately.

The number of patients with study drug disruption due to COVID-19 will be provided as well. The number of patients with TEAEs related to corona virus infection or coronavirus test positive will be provided. Supporting listings for the described analyses above will be provided.

18.0   CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

None.

19.0 REFERENCES

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20.0 APPENDICES

APPENDIX I. PATTERN-MIXTURE MODEL DETAILS

For repeated measures with the monotone missing mechanism, the pattern-mixture model with non-future dependent missing assumption, proposed by Kenward et at. (2003), provides a feasible solution to accommodate certain missing not at random (MNAR) mechanism. The methodology relies on constructing unidentifiable conditional densities using identifiable densities and borrows techniques from standard multiple imputation.

1. Non-Future Dependent Missing Assumption

Assume there are T designed visits in a longitudinal study and let $y_i \, (i = 1,2,...,T)$ represent patient's measurement at Visit i. When the missing mechanism is monotone, the pattern of missing data can be defined by the number of measurements (L) actually observed from the patient. Let $f(y_i,...,y_j \mid L = t)$ denote the conditional density of $y_i,...$ y_j, given that the last observed measurement is at Visit t. Then the overall density function for Pattern t can be written as

$$f(y_1,..., y_T \mid L = t) = f(y_1,..., y_t \mid L = t) f(y_{t+1} \mid y_1,..., y_t, L = t)$$
$$\times \prod_{s = t+2}^{T} f(y_s \mid y_1,..., y_{s-1}, L = t) \qquad (1)$$

Note on the right hand side of (1) the first factor is clearly identifiable from the observed data, while the second and the beyond are not, due to lack of available data. The second factor $f(y_{t+1} \mid y_1,...,y_t, L = t)$ could be identifiable based on an assumed relationship between $f(y_{t+1} \mid y_1,...,y_t, L = t)$ and $f(y_{t+1} \mid y_1,...y_t, L \geq t + 1)$. The third and beyond factors $f(y_s \mid y_1,...,y_{s-1}, L = t)$ (with all $s \geq t + 2$) could be identifiable with the help of non-future dependent missing assumption.

For longitudinal data with dropouts, non-future dependent (NFD) missing mechanism (Kenward et al., 2003) assumes that the unidentifiable conditional distributions of y_s ($s \geq t + 2$), given earlier measurements, in Pattern t, is equal to the corresponding distribution in patterns $L \geq s - 1$:

$$f(y_s \mid y_1,..., y_{s-1}, L = t) = f(y_s \mid y_1,..., y_{s-1}, L \geq s - 1) \qquad (2)$$

The right hand side of (2) can further be partitioned into

$$f(y_s \mid y_1,..., y_{s\text{-}1}, L \geq s-1) = \sum_{j=s\text{-}1}^{T} \omega_{s\text{-}1,j} \cdot f(y_s \mid y_1,..., y_{s\text{-}1}, L = j) \qquad (3)$$

Where mixture probabilities $\omega_{s\text{-}1,j}$ are:

$$\omega_{s\text{-}1,j} = \frac{\alpha_j f(y_1,...,y_{s\text{-}1} \mid L = j)}{\sum\limits_{t=s\text{-}1}^{T} \alpha_t f(y_1,...,y_{s\text{-}1} \mid L = t)}, \quad \text{and } \alpha_j \text{ represents the fraction of} \qquad (4)$$

patients from Pattern j.

Each factor of the unidentifiable conditional distribution of y_s $(s \geq t + 2)$ on the right side of (1) can be expressed using the following:

- $f(y_s \mid y_1,..., y_{s-1}, L = s-1)$, the unidentifiable conditional distribution of the first missing in pattern $s-1$,

- $f(y_s \mid y_1,..., y_{s-1}, L = j)$, the identifiable conditional distributions of y_s given $y_1,..., y_{s-1}$ of pattern j $(j \geq s)$, and

- α_j, the fraction of patients from pattern j $(j \geq s - 1)$.

So under NFD, all the unidentifiable conditional distribution on the right side of (1) can be estimated and missing value could be therefore imputed based on the assumption for unidentifiable conditional distribution of the first missing.

We re-formulate the partition in (3), for $s \geq t+2$, as the following:

$$f(y_s \mid y_1,..., y_{s\text{-}1}, L = t) = \delta_{s\text{-}1} f(y_s \mid y_1,..., y_{s\text{-}1}, L = s-1) \qquad (5)$$
$$+ (1 - \delta_{s\text{-}1}) f(y_s \mid y_1,..., y_{s\text{-}1}, L \geq s)$$

for $s \geq t+2$ with $\delta_{s-1} = \omega_{s-1,s-1}$.

Therefore, under monotone missing and NFD assumption, the unidentifiable conditional densities for Visit s in Pattern t ($s \geq t + 2$) can be expressed as a mixture distribution of $f(y_s \mid y_1, ..., y_{s-1}, L = s - 1)$ - the unidentifiable conditional distribution of the first missing measurement y_s in Pattern $s - 1$, and $f(y_s \mid y_1, ..., y_{s-1}, L \geq s)$ - the identifiable conditional distribution of y_s from all the patterns with observed data at Visit s or beyond:

$$f(y_s \mid y_1, ..., y_{s-1}, L \geq s) = \sum_{j = s}^{T} \lambda_{s-1,j} f(y_s \mid y_1, ..., y_{s-1}, L = j) \qquad (6)$$

where the mixture probability

$$\lambda_{s-1,j} = \omega_{s-1,j} / (1 - \omega_{s-1, s-1}) =$$

$$\frac{\alpha_j f(y_1, ..., y_{s-1} \mid L = j)}{\sum_{t = s}^{T} \alpha_t f(y_1, ..., y_{s-1} \mid L = t)} \quad \text{for } j \geq s, \text{ where } \alpha_j \text{ is the fraction of} \qquad (7)$$

patients from Pattern j.

The conditional densities for the first missing are selected as:

$$f(y_s \mid y_1, ..., y_{s-1}, L = s - 1) = f(y_s - \Delta \mid y_1, ..., y_{s-1}, L \geq s) \text{ for } s = 2, ..., T, \quad (8)$$

Note that the two distributions only differ by a shift (Δ) parameter. When $\Delta = 0$, the missing value y_s in Pattern s-1 is imputed based on the distribution of all observed data up to Visit s, as a result, leading to missing at random (MAR) missingness. When $\Delta \neq 0$, (8) will introduce a scenario of MNAR. The similar idea was also presented in the recent publication "The Prevention and Treatment of Missing Data in Clinical Trials" by the National Academies Press. The selection of the plausible values for the shift parameter (Δ) is discussed in Section 3.0.

Note that per recommendation in Wang and Daniels (2011), only the observed data within pattern is assumed to be multivariate normal. The observed data distribution can be expressed in terms of the marginal distribution of baseline measurement and the conditional distributions of postbaseline measurements given earlier measurements. Assuming that these distributions are normal, the linear regression of each observation on prior observations will yield least-squares estimates of model parameters that can be utilized for independent posterior draws of model parameters for observed data. Multiple imputation approach will be used to estimate the overall mean at the final time point.

2.   Imputation Procedure

All the missing data will be imputed to create complete datasets, then statistical analysis can be performed using appropriate techniques such as ANCOVA. The imputation can accommodate MNAR missing data mechanisms, based on the theory discussed in the previous section.

The model parameters for each dropout pattern, i.e., the mean, variance and proportions of observations in each pattern, are drawn from their posterior distributions prior to the imputation of missing data for a single imputation.

The details of imputation within a pattern, say Pattern t, are as the following:

Step 1. Impute the first missing value y_{t+1} for each patient in Pattern t $(t = 1,..., T-1)$:

a. Compute estimates of mixture probabilities $\lambda_{s-1,j}$ in (7) with $s = t+1$ given the posterior draw of proportions of observations in each pattern and the posterior draw of regression parameters for the observed data.

b. Draw a random integer from $\{s,...,T\}$ to index a component distribution on the right hand side of (6), using mixture probabilities obtained in a). Draw y_{t+1}^{*} from the identified component normal distribution. Impute the missing y_{t+1} as $\tilde{y}_{t+1} = y_{t+1}^{*} + \Delta$.

Step 2. Impute the rest of the missing values of $y_{t+2}, y_{t+3}, ..., y_T$ for patients in Pattern t:

Starting with imputation for y_{t+2}, first, similar to Step 1, draw y_{t+2}^{*} from the normal mixture (6) based on the observed $y_1,...,y_t$ and the already imputed $\tilde{y}_{t+1}$ for the patient. Then the missing y_{t+2} is imputed as $\tilde{y}_{t+2} = y_{t+2}^{*} + \Delta$ with probability δ_{t+1} and as $\tilde{y}_{t+2} = y_{t+2}^{*}$ with probability $1 - \delta_{t+1}$, where the mixture probability $\delta_{t+1} = \omega_{t+1,t+1}$ is obtained from (4) given the posterior draw of proportions of observations in each pattern and the posterior draw of regression parameters for the observed data.

Missing values of y_{t+3} through y_T can be imputed similarly as y_{t+2}.

To summarize, the imputations of y_{t+1} through y_T is done recursively within each Pattern t (for all $t = 1,...,T-1$) to create a complete dataset after imputation is done for all patterns with missing values.

The above imputation procedure is applied to all subjects in each missing data pattern to create a single imputed data set. Repeating the process of drawing parameters from the posterior distribution and imputing missing data given the posterior draw m times will yield m imputed data sets. The observed or imputed values at the final data point are averaged to obtain the overall mean estimate for each imputed data set, and the multiple imputation estimate is obtained by averaging the estimates across m imputations.

In this sensitivity analysis, m is set to equal to 20. The value of m is discussed in the context of imputation efficiency in standard multiple imputation theory (Rubin, 1987, p. 114), and m = 20 would provide at least 96% of relative efficiency as compared with using a large number of imputations (SAS/STAT User's Guide, p. 3796).

3.   Determination of the Shift Parameter Values

The common shift parameter Δ is the difference between the mean of y_{t+1} among those who drop out at Visit t and those who remain beyond Visit t ($1 \leq t \leq T - 1$). The exact value of Δ is unknown and can't be estimated from data because of missingness. The magnitude of Δ depends on the medical aspects of the trial. Using relevant historical data, one may select Δ as a proportion of the sample standard deviation or a proportion of observed treatment efficacy.

References:

Kenward MG, Molenberghs G, Thijs H. Pattern-mixure models with proper time dependence. *Biometrika,* 2003;90:53-71.

Rubin DB. Multiple Imputation for Nonresponse in Surveys. J. Wiley & Sons, New York; 1987.

SAS Institute Inc. SAS/STAT 9.2 User's Guide, Second Edition. Cary, NC: SAS Institute Inc; 2009.

Wang C, Daniels MJ. A note on MAR, identifying restrictions, model comparison, and sensitivity analysis in pattern mixture models with and without covariates for incomplete data. *Biometrics,* 2011; 67(3):810-818.

APPENDIX II. REPORTING SELECTED LABORATORY PARAMETERS IN CONVENTIONAL UNIT

All clinical laboratory parameters will be reported in the International System (SI) units as standard practice. In addition, descriptive statistics for values and changes from baseline in conventional units at all assessed visits will be reported for selected laboratory parameters as listed in Table 20–1 below.

Table 20–1.   List of Selected Parameters to be Reported in Conventional Units

Number	Laboratory Parameter	Conventional Unit
1	Alanine Aminotransferase (SGPT)	U/L
2	Albumin	G/dL
3	Alkaline Phosphatase	U/L
4	Aspartate Aminotransferase (SGOT)	U/L
5	Bilirubin, Direct (Conjugated)	mg/dL
6	Bilirubin, Indirect (Unconjugated)	mg/dL
7	Bilirubin, Total	mg/dL
8	Blood Urea Nitrogen	mg/dL
9	Calcium	mg/dL
10	Cholesterol, HDL	mg/dL
11	Cholesterol, LDL	mg/dL
12	Cholesterol, LDL direct and calculated (combined) *(This lab parameter could be the same as #11)*	mg/dL
13	Cholesterol, Total	mg/dL
14	Creatine Kinase	U/L
15	Creatinine	mg/dL
16	Glucose	mg/dL
17	Insulin	uIU/mL
18	Triglycerides	mg/dL
19	Uric Acid	mg/dL
20	Hemoglobin	G/dL

APPENDIX III.   STATISTICAL ANALYSIS LIST FOR FUTILITY ANALYSIS

Table 20–2   List of Statistical Analysis for Futility Analysis

Table ID	Title	Analysis Population
14.1-1.1	Disposition of Participants	Screened Population
14.1-4.1.1A	Demographics	Safety Population
14.1-4.1.3	Baseline Characteristics and Efficacy Variables	Intent-to-Treat Population
14.2-1.1	CDRS-R Total Score: Summary of Baseline, Post-baseline and Analysis of Change from Baseline - MMRM	Intent-to-Treat Population
14.2-2.1	CGI-S Score: Summary of Baseline, Post-baseline and Analysis of Change from Baseline - MMRM	Intent-to-Treat Population
14.3-1.1	Extent of Exposure	Safety Population
14.3-2.1.A	Adverse Events: Overall Number (%) of Participants with Adverse Events During the Double-Blind Treatment Period	Safety Population
14.3-2.2.A	Treatment-Emergent Adverse Events: Number (%) of Participants with Treatment-Emergent Adverse Events During the Double-Blind Treatment Period by Treatment Group, System Organ Class and Preferred Term	Safety Population
14.3-2.3.A	Common ($\geq$ 2%) Treatment-Emergent Adverse Events: Number (%) of Participants by Preferred Term During the Double-blind Treatment Period	Safety Population
14.3-4.1	Laboratory Parameters: Number (%) of Participants with Post-baseline Potentially Clinically Significant Values During the Double-blind Treatment Period	Safety Population
14.3-5.1	Vital Sign Parameters: Number (%) of Participants with Post-baseline Potentially Clinically Significant Values During the Double-blind Treatment Period	Safety Population
14.3-6.1	ECG Parameters: Number (%) of Participants with Post-baseline Potentially Clinically Significant Values	Safety Population
14.3-7.2.A	C-SSRS: Number (%) of Patients with Suicidal Ideation or Suicidal Behavior During the Double-blind Treatment Period	Safety Population
* Table IDs are based on the Study SAP TFL shell document.		

APPENDIX IV.   CONDITIONAL POWER CALCULATION

Conditional power is defined as the probability of rejecting H_0 at the end of the trial when total information is obtained, conditional on the partial information accumulated up to that point.

Suppose that the final analysis is a Z test based on a total of N observations, denoted as Z_N and we compare it with the critical value 1.96 that is for the significance level of 0.025 of a one-sided Z test at the end of trial.

At the interim stage, suppose there are N_1 observations; z_1 is the Z statistics; $\hat{\delta}_1$ is the observed treatment different; I_1 is the information at the interim analysis; u_2 is the final efficacy boundary value (u_2 =1.96 for futility interim); I_2 is the total maximum information. The conditional power at hypothesized $\hat{\delta}_1$ is as following,

$$CP(\hat{\delta}_1, z_1) = \Phi \left\{ \frac{z_1\sqrt{I_1} - u_2\sqrt{I_2} + (I_2 - I_1)\hat{\delta}_1}{\sqrt{I_2 - I_1}} \right\}$$

The way we calculate the I_1 and I_2 in conditional power follows the EAST method, using the estimated standard error se_1 $\hat{\sigma}^2$ at the interim look. Let $\hat{\sigma}_1$ denote the estimated standard deviation at the interim, then $\hat{\sigma}_1 = se_1\sqrt{N_1/4}$, and then we have

$$I_1 = \frac{N_1}{4\hat{\sigma}_1^2} \quad \text{and} \quad I_2 = \frac{N}{4\hat{\sigma}_1^2}.$$

APPENDIX V.   SUMMARY OF CHANGES FOR AMENDMENT #1

Amendment #1 specifies the following changes to the Statistical Analysis Plan for LVM-MD-14 dated in 15 July 2019.

1. Add the sensitivity analysis in Section 10.1 for the site 0070.

2. Update the Section 13.0 Interim Analysis to add the futility analysis

3. Update the Section 17.0 to COVID-19 related analysis

4. Add the Appendix III to statistical analysis list for futility analysis

5. Add the Appendix IV to conditional power calculation

The details related to content changes are provided below. Minor editorial and document formatting revisions have not been summarized.

Section 10.1 Primary Efficacy Parameter(s)

The site 0070 ceased operations on October 31, 2020, due to the damage caused by Hurricanes Laura and Delta, which made landfall on August 27, 2020 and October 10, 2020, respectively. One more sensitivity analysis excluding all data from this site will be performed on the primary efficacy parameter. The same MMRM would be applied on all OC of change from baseline to Week 8 in CDRS-R total score except all values of Site 0070.

Section 13.0 Interim Analysis

~~No interim analysis is planned for this study.~~

Revised text reads as follows:

The interim analysis will be conducted when at least 50% of randomized patients have either completed or discontinued the study. A futility analysis and safety analysis will be included in the interim analysis listed in the Appendix III. The general data derivation and preparation will follow the specification in the SAP and the amendment.

The futility assessment of the primary efficacy parameter (CDRS-R total score) on ITT population will be based on the conditional power as described in Lan et al. (1988) and Proschan et al. (2006). In calculating the conditional power, it is assumed that the future patients to be enrolled into the Study will have similar efficacy as those of the existing patients of the same treatment group. The non-binding futility criteria will be met when the conditional power for detecting a statistically significant treatment difference between the levomilnacipran treatment group (40-80 mg/day) and placebo at the final analysis given the interim analysis results is 0.2 (20%) or lower. Further details of the calculation of conditional power are provided in Appendix IV.

The safety analysis will be performed on the Safety Population, including the summary of TEAE, SAE, death, and TEAE leading to study discontinuation; the incidence of common TEAEs ($\geq 2\%$); PCS for laboratory parameters, vital signs, and ECGs; and the summary of C-SSRS during the double-blind treatment period.

Data will be presented in an unblinded fashion. A separate, independent, fire-walled Statistical Analysis Group and Data Review Committee will be established to conduct the unblinded interim analysis, review the unblinded results and make recommendations regarding the continuation of the study. To maintain the scientific reliability of statistical analyses after the final database lock, preserve the integrity of study conduct, and guard from introducing any potential bias into the conduct of the study and/or analysis of its results, individuals in these two groups will not be involved in any operational aspects of the trial.

Section 17.0 COVID-19 Related Analysis

To eliminate immediate potential hazards to patients and study staff due to the COVID-19 pandemic while ensuring patients safety and maintaining data integrity, a protocol amendment was sent to sites to allow remote visits.

This section specifies analyses for evaluating the impact of COVID-19.

Section 17.1 Efficacy Evaluation

Due to the nature of the patient CDRS-R assessment, the interview may be performed remotely provided that the patient has access to a videoconferencing platform where the rating clinician can visually see the patient during the discussion. Minimal disruption is expected for this endpoint.

Section 17.2 Safety and Other Evaluation

This section specifies analyses related to the COVID-19 pandemic from the following aspects:

- Disposition

- Study visit (missing entire visit due to COVID-19 or missing assessments due to COVID-19)

- Protocol deviation

- Study drug disruption due to COVID-19

- TEAEs related to COVID-19

The Safety Population will be used for the planned analyses described above.

The number of patients impacted by COVID-19 during the study will be summarized by treatment group and overall. In addition, the number of patients impacted by COVID-19 and their corresponding disposition status in the double-blind treatment period, down-taper period, and follow-up period will be summarized, respectively.

The number of patients who missed at least one entire visit due to COVID-19 will be summarized by treatment group and overall. Furthermore, the number of patients who missed at least one assessment due to COVID-19 will be summarized by assessment category (laboratory, C-SSRS, vital signs, and ECG) and overall. Similar summarized will by provided by visit.

Appendix III. Statistical Analysis List for Futility Analysis

Table 20-2.   List of Statistical Analysis for Futility Analysis

Table ID	Title	Analysis Population
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14.3-2.2.A	Treatment-Emergent Adverse Events: Number (%) of Patients with Treatment-Emergent Adverse Events During the Double-Blind Treatment Period by Treatment Group, System Organ Class and Preferred Term	Safety Population
14.3-2.3.A	Common ($\geq$ 2%) Treatment-Emergent Adverse Events: Number (%) of Patients by Preferred Term During the Double-blind Treatment Period	Safety Population
14.3-4.1	Laboratory Parameters: Number (%) of Patients with Post-baseline Potentially Clinically Significant Values During the Double-blind Treatment Period	Safety Population
14.3-5.1	Vital Sign Parameters: Number (%) of Patients with Post-baseline Potentially Clinically Significant Values During the Double-blind Treatment Period	Safety Population
14.3-6.1	ECG Parameters: Number (%) of Patients with Post-baseline Potentially Clinically Significant Values	Safety Population
14.3-7.2.A	C-SSRS: Number (%) of Patients with Suicidal Ideation or Suicidal Behavior During the Double-blind Treatment Period	Safety Population
* Table IDs are based on the Study SAP TFL shell document.		

Appendix IV. Conditional Power Calculation

Conditional power is defined as the probability of rejecting H0 at the end of the trial when total information is obtained, conditional on the partial information accumulated up to that point.

Suppose that the final analysis is a Z test based on a total of N observations, denoted as ZN and we compare it with the critical value 1.96 that is for the significance level of 0.025 of a one-sided Z test at the end of trial.

At the interim stage, suppose there are N1 observations; z1 is the Z statistics; $\hat{\delta}_1$ is the observed treatment different; I1 is the information at the interim analysis; u2 is the final efficacy boundary value (u2 =1.96 for futility interim); I2 is the total maximum information. The conditional power at hypothesized $\hat{\delta}_1$ is as following,

$$CP\left(\hat{\delta}_1, z_1\right) = \Phi\left\{\frac{z_1\sqrt{I_1} - u_2\sqrt{I_2} + (I_2 - I_1)\hat{\delta}_1}{\sqrt{I_2 - I_1}}\right\}$$

The way we calculate the I1 and I2 in conditional power follows the EAST method, using the estimated standard error se1 $\hat{\sigma}^2$ at the interim look. Let $\hat{\sigma}_1$ denote the estimated standard deviation at the interim, then $\hat{\sigma}_1 = se_1\sqrt{N_1/4}$, and then we have

$$I_1 = \frac{N_1}{4\hat{\sigma}_1^2} \quad \text{and} \quad I_2 = \frac{N}{4\hat{\sigma}_1^2}.$$